Neuroimaging of Vascular Dementia

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INTRODUCTION

Cerebrovascular disease (CVD) is the second most prominent cause of dementia either alone or in combination with Alzheimer disease (AD).1 In the past, the term vascular dementia (VaD) was used to define the cognitive impairment resulting from CVD and ischemic or hemorrhagic brain injury.2 The definition and diagnostic criteria of VaD remains unclear and generates much confusion in clinical practice. In addition, it was not able to classify patients who develop a cognitive impairment that does not fulfill the traditional criteria for dementia but that nonetheless has a significant impact on the patients’ quality of life and ability to carry out activities of daily living. The term vascular cognitive impairment (VCI) was introduced to encompass all of the effects of vascular diseases or lesions on cognition and incorporate the complex interactions between vascular causes, risk factors, and cellular changes within the brain and cognition.3 VCI refers to “a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain.” VCI also includes both pure (CVD alone) and mixed (CVD with other pathologic conditions, such as that of AD). It is important to understand that VCI is not a disease like AD but is rather a syndrome or phenotype that results from CVD, subsequently leading to vascular brain injury that disrupts the brain network for memory and thinking. VaD is a subset of the broader designation VCI.

PREVALENCE

Dementia from all causes has a prevalence of about 8% in individuals aged more than 65 years.1,3 In the Western literature, VaD is the third leading cause of progressive and irreversible dementia after Alzheimer disease (60%–70%) and dementia with Lewy bodies (10%–25%).

KEY POINTS

- Vascular dementia (VaD) is the third leading cause of progressive and irreversible dementia after Alzheimer disease (60%–70%) and dementia with Lewy bodies (10%–25%).
- Because of the high variability of cerebrovascular pathologic conditions and its causative factors, there are no accepted neuropathologic criteria for diagnosing VaD.
- Brain pathology may show diffuse confluent age-related white matter changes, multi-lacunar state (état lacunaire), multiple (territorial) infarcts, strategic cortical-subcortical or watershed lesions, cortical laminar necrosis (granular cortical atrophy), and delayed postischemic demyelination and hippocampal sclerosis.
- Subcortical VaD is the most common subtype of small-vessel VaD and constitutes approximately 50% of VaD cases.

KEYWORDS

- Vascular dementia
- MR imaging
- Subcortical vascular dementia
- CADASIL
- Cerebral amyloid angiopathy (CAA)

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dementia after AD (60%–70%) and dementia with Lewy bodies (10%–25%). The incidence of VaD shows a wide variation in the patient population (age, sex), geographic location, and use of clinical methods. Of all causes of dementia, 13% to 19% are from pure vascular causes, whereas mixed dementia whereby vascular causes are part of the disease is seen in 11% to 43%. The proportion of cases caused by VaD decreases with increasing age, but the prevalence of all dementia increases so rapidly with age that the prevalence of VaD also increases, from 0% to 2% in the 60- to 69-year-old age group and up to 16% (3%–6% for men) in individuals aged 80 to 89 years. Globally, VaD seems to be more common in men, especially before 75 years of age. The incidence in women and men aged 85 years and older is around 9.3% and 15.9%, respectively. Epidemiologic studies suggest that the incidence of VaD in Europe accounts for about 15% to 20% of the cases, whereas in Japan it accounts for around 50% of the cases. VaD is also more prevalent in populations affected by cerebral small-vessel disease (SVD), such as Asians, African Americans, and Hispanics.

The introduction of the new term VCI encompasses all of the effects of vascular disease on cognition leading to a change in the epidemiology. In patients younger than 74 years, VCI may be the single most common cause of cognitive impairment. In those individuals aged 75 to 84 years, cases of pure VCI, VaD, and those with a vascular component in the context of mixed disease outnumber those with pure AD. In a Canadian study, the prevalence of VCI has been estimated at 5% in people older than 65 years. The cognitive outcome of patients with VaD may be as severe as in AD, but their morbidity and mortality are usually worse.

**DIAGNOSTIC CRITERIA**

The concept of CVD leading to cognitive decline and dementia has been recognized since the seventeenth century. In the latter half of the nineteenth century, Kraepelin and colleagues coined the term *atherosclerotic dementia*. In 1974, Vladimir Hachinski and colleagues introduced the term *multi-infarct dementia* (MID). Since then, because of the advances in imaging techniques, our understanding of the disease process has significantly evolved. Unfortunately, because of the high variability of cerebrovascular pathologic conditions and its causative factors, there are no accepted neuropathologic criteria for diagnosing VaD or VCI, as agreed for AD or dementia with Lewy bodies. Unlike AD, vascular lesions are classified based on the morphologic characteristics rather than by their pathogenesis. The criteria from the *Diagnostic and Statistical Manual of Mental Disorders, (Fourth Edition) (DSM-IV)* for VaD were proposed by the American Psychiatric Association from a general definition of dementia (Box 1). The major limitations for these criteria are the following: They are purely clinical. No neuroimaging findings are incorporated. No criteria are mentioned to establish a causal relationship between dementia and vascular disease. The cross-sectional neuroimaging modalities computed tomography (CT) and magnetic resonance (MR) imaging have significantly improved our understanding of SVD, MID, and VaD. In 1993, the National Institute of Neurologic Disorders and Stroke (NINDS–Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) formulated criteria that incorporated the structural neuroimaging as a crucial element for the diagnosis of VaD (Box 2). To enhance their clinical implementation, operational definitions for the radiological part of the NINDS-AIREN’s criteria were subsequently modified in 2003. To diagnose VaD, the current criteria require the presence of the syndrome of dementia and a pathophysio-

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**Box 1**

**DSM-IV criteria for VaD**

a. There are multiple cognitive deficits manifested by both memory impairment and one or more of the following cognitive disturbances: aphasia, apraxia, agnosia, or disturbance in executive functioning.

b. The cognitive deficits cause significant impairment in social or occupational activities and represent a significant decline from a previous level of functioning.

c. There are focal neurologic signs and symptoms (eg, exaggeration of deep tendon reflexes, extensor plantar response, pseudo-bulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicating CVD (eg, multiple infarcts involving the cortex and the underlying white matter) that are judged to be etiologically related to the disturbance.

d. The deficits do not exclusively occur during the course of a delirium.

The risk factors for VCI are the same as that for CVD, stroke, and white matter lesions (WMLs), which include arterial hypertension, atrial fibrillation, myocardial infarction, coronary artery disease, diabetes, generalized atherosclerosis, lipid abnormalities, smoking, family history, and specific genetic features. The pathophysiology of VCI and VaD is thought to be multifactorial and is attributed to causes like CVD, infarcts, diffuse WMLs, atrophy, and host factors. These lesions are either diffuse or in the strategic location and cause interruptions of the various white matter tracts and cortical and subcortical neuronal circuits leading to various cognitive declines and dementia. The neuropathologic changes associated with VaD include multifocal and/or diffuse disease or as a single focal lesion in the strategic location. Brain pathology may show diffuse confluent age-related white matter changes, multi-lacunar state (état lacunaire), multiple (territorial) infarcts, strategic cortical-subcortical or watershed lesions, cortical laminar necrosis (granular cortical atrophy), and delayed postischemic demyelination and hippocampal sclerosis. It is the combinations of these findings seen that often
cause the cognitive decline. Histopathology specimens show cellular processes, such as demyelination, axonal damage, diaschisis or retrograde degeneration, and atrophy.

At the neurotransmitter level, cholinergic dysfunction has been well documented in the experimental animal models of ischemic VaD. Deficits in cholinergic markers and cholinergic receptors have also been documented in human cases of VaD. These changes are most pronounced in the basal forebrain nuclei, which are supplied by penetrating arterioles from the middle cerebral artery (MCA), anterior communicating artery, and anterior cerebral artery (ACA). In addition, vascular insults affecting the white matter and basal ganglia can also interrupt the cholinergic projections from the basal forebrain.

NEUROIMAGING

The imaging appearance of VaD can be broadly divided into (1) large-vessel VaD, (2) small-vessel VaD, and (3) microhemorrhage and dementia (Box 3).

LARGE-VESSEL VA D

**MID (Poststroke Dementia)**

Large-vessel VaD may be either caused by multiple or single cortical or subcortical infarcts or caused by a cerebrovascular lesion involving the strategic regions like the hippocampus, parietal thalamus, and thalamocortical networks. The source of these infarcts may be due to atherosclerosis, vasculitis, or embolic phenomenon. Occlusion of the extracranial arteries, the internal carotid artery, the main intracranial arteries including the MCA, medium-sized arteries in the leptomeninges, and proximal perforating arteries can lead to VaD. The damage can be worse depending on the presence of hypertension and related CVD. The NINDS-AIREN’s criteria define probable VaD as a cognitive decline from a previously higher level of functioning in memory and 2 or more cognitive domains, with the decline being severe enough to interfere with activities of daily living. For the diagnosis of the VaD, both clinical criteria and neuroimaging evidence of CVD are required. The clinical criteria may have 2 of the following: (1) onset of dementia within 3 months after a recognized stroke, (2) abrupt deterioration in cognition (days to weeks), and/or (3) stepwise deterioration. Imaging plays a supportive role by identifying the type (hemorrhagic vs nonhemorrhagic) and localizing the anatomic site of the abnormality.

VaD largely depends on the site of the blocked vessel and the affected brain parenchyma. Up to one-third of stroke survivors exhibit dementia within 3 months after their stroke, whereby memory loss may not be the primary symptom. In classic poststroke patients, cortical cognitive deficits, such as agnosia, apraxia, alexia, aphasia, and visuospatial or constructional difficulty, are seen, often without motor deficit.

Cross-sectional imaging with CT and MR along with CT angiography or MR angiography have become the imaging modalities to evaluate patients with VaD. These modalities are very sensitive in confirming the size and location of the symptomatic as well as asymptomatic (silent) strokes. MR is also very helpful in the diagnosis of microbleeds, anoxic/hypoxic brain injury, and identifying the changes of gliosis and encephalomalacia. The parenchymal perfusion status may also be obtained using CT or MR perfusion. Diffusion-weighted imaging (DWI)–apparent diffusion coefficient (ADC) has an established role in the diagnosis of hyperacute infarction. An infarcted area, which has a decrease in Brownian motion, is seen on the DWI sequence as restricted diffusion with low ADC. In the subacute-chronic stage of infarction, imaging is characterized by local brain atrophy, gliosis, cavity formation, and ex vacuo dilatation of the ipsilateral ventricle. Encephalomalacia and gliosis are seen on T2 and fluid-attenuated inversion recovery (FLAIR) images.
as a loss of parenchymal tissue with hyperintensity in the infarcted and subjacent tissue with prominence of cerebrospinal fluid (CSF) space (Fig. 1). Calcification and deposition of blood products (hemosiderin) may be seen on T2 and gradient echo (GRE) sequences. Corticospinal tract degeneration (ie, Wallerian degeneration) is also seen with hemispheric infarction. There is a loss of brain tissue and its corresponding function. Strokes involving the left hemisphere were shown to have a higher incidence of dementia as compared with the right. Also, a strong correlation is seen between dementia and infarctions in the left posterior cerebral artery (PCA) and the ACA and parietal areas (Fig. 2). Cortical laminar necrosis, neuronal ischemia accompanied by gliosis, and layered deposition of fat-laden macrophages may be seen in the infarcted region. Gray matter is more vulnerable to hypoxia than white matter. On MR, laminar necrosis is seen as hyperintensity in the cortex on T1-weighted and FLAIR images (Fig. 3). These changes are visible 2 weeks after infarction and are most prominent at 1 to 3 months.

Watershed Infarctions

Watershed infarctions are seen at the junction of the distal fields of the 2 nonanatomizing major cerebral arteries. They are classified into cortical and internal watershed infarcts. Cortical watershed infarcts may occur symmetrically or unilaterally in circular border zones between the deep and superficial branches of ACA, MCA, and PCA. The pathogenesis of watershed infarction remains debatable and is thought to be multifactorial. A hemodynamic mechanism, which includes internal carotid stenosis or occlusion, systemic

Fig. 1. Chronic right MCA infarction with severe cognitive decline. Axial FLAIR (A–C) MR images show large chronic right MCA infarct with encephalomalacia and surrounding hyperintensity caused by gliosis (fat arrows). There is ex vacuo dilatation of the ipsilateral lateral ventricle. There is atrophy of the right side of the brainstem with hyperintensity in the cerebral peduncles caused by Wallerian degeneration (small arrow in C). Also seen is severe atrophy of the head and body of the right hippocampus (arrowheads in C).
hypotension, and embolic events, is a major cause of watershed infarction. They are caused by hypotension with misery perfusion (ie, diminished flow in distal vessels or showers of microemboli).\textsuperscript{21} Watershed infarction may affect eloquent areas of the brain and may be associated with a strategic infarct dementia. The superior frontal area, between the distal supply of the ACA and MCA, and the posterior parieto-occipital junction, among ACA, MCA, and PCA, are frequently involved with watershed infarction. Associated hypoxia may also cause alterations in the hippocampal subareas CA-1 and CA-4, the outer half of the caudate nucleus and putamen, and the anterior and dorsomedial nucleus of the thalamus. Damage to these areas is often associated with the development of cognitive decline and dementia.

MR is very sensitive and specific in the diagnosis of watershed infarction. In acute events, DWI is very sensitive for the diagnosis of both cortical watershed infarct and internal watershed infarct. Classically, cortical watershed infarcts appear as fan- or wedge-shaped hyperintensities extending from the lateral margins of the lateral ventricle toward the cortex, whereas internal watershed

![Fig. 2. PCA infarct in a 69-year-old male patient with dementia. Axial T2 (A) and FLAIR (B) MR images show a large left temporo-occipital chronic infarct with mild ex vacuo dilatation of the temporal horn (thin arrow). There is mild volume loss of the head of left hippocampus (fat arrow).](image)

![Fig. 3. Laminar necrosis. Axial T1 (A) and FLAIR (B) MR images reveal large chronic left MCA infarction with encephalomalacia and gliosis. Hyperintensity seen along the gyri on T1 and FLAIR images within the infarcted area is suggestive of cortical laminar necrosis (arrows).](image)
Infarcts are seen as hyperintensities running parallel to the lateral ventricles, either confluent or focal, and may be unilateral or bilateral (Fig. 4).\textsuperscript{22}

**Strategic Single-Infarct Dementia**

Strategic infarct dementia is characterized by focal, ischemic lesions in areas that control or participate in cognition and behavior or higher cortical functions. The strategic cortical sites include the hippocampal formation, angular gyrus, and cingulate gyrus, whereas the subcortical sites leading to impairment are the thalamus, fornix, basal forebrain, caudate, globus pallidus, and the genu or anterior limb of the internal capsule.\textsuperscript{23} The mechanism by which the strategic single infarct leads to dementia is not completely understood, but it is thought to be caused by the interruption of frontal-subcortical circuits.\textsuperscript{11,24}

The general organization of these circuits includes the frontal lobes, striatum, globus pallidus/substantia nigra, and the thalamus.

Cognitive decline and the clinical symptoms largely depend on the strategic area involved. Caudate nucleus infarctions can lead to abulia, restlessness and hyperactivity, language deficits, and poor memory. The cognitive domains mostly affected in caudate infarcts are decreased problem-solving ability, impaired recent and remote memory with preservation of recognition memory, and decreased attention. Ischemic stroke or a subarachnoid hemorrhage from ruptured aneurysms involving the mesial temporal lobe and thalamus may cause memory and other

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**Fig. 4.** Watershed infarct with dementia. Axial DWI (A) and FLAIR (B) MR images show bilateral deep cortical watershed infarctions bilaterally (arrowheads). Sixteen months following the event, the patient presented with gradual cognitive decline. Axial FLAIR (C) MR image shows mild global atrophy with diffuse white matter changes (arrows) suggestive of chronic microangiopathic changes.
cognitive deficits because of the interruption of the cholinergic projections to the cholinergic nuclei in the basal forebrain (Fig. 5). These patients may present with severe anterograde amnesia for verbal or visuospatial material, along with severe apathy, lack of initiative and spontaneity, and executive dysfunction. These patients are also unable to encode and consolidate new verbal material, such as facts, events, short stories, names, and concepts. This inability may be difficult clinically to differentiate from AD. A thalamic stroke produces a peculiar form of thalamic VaD (Fig. 6). These patients show a depressed level of consciousness impairments in attention, motivation, initiative, executive functions, and memory, as well as dramatic verbal and motor slowness and apathy. Thalamic lesions may cause thalamic amnesia because of the damage to the mammillothalamic tract; even small and/or unilateral damage to this structure may affect memory, executive functioning, and attention. PCA infarcts may cause damage to the hippocampus, isthmus, entorhinal and perirhinal cortex, and parahippocampal gyrus (see Fig. 2). Therefore, patients may present with amnesia.

**Hypoperfusion and Ischemic Encephalopathy**

Diseases of the large arteries and the heart can lead to cerebral hypoperfusion and have been associated with the development of dementia after stroke. Hypoperfusion may affect both gray and white matter. Hypoperfusion affecting white matter may lead to leukoaraiosis and incomplete infarction, which comprises zones of partial neuronal or axonal loss with demyelination, increased perivascular spaces, reactive astrocytosis, and gliosis. Damage to the cerebral cortex with laminar necrosis may be seen at the arterial border zones following hypoxia. These zones are

![Fig. 5. Chronic right temporal lobe infarction with severe memory loss. Axial FLAIR (A), sagittal T1 (B), and coronal T1 (C) MR images show chronic infarction of the anterior temporal lobe with ex vacuo dilatation of the right temporal horn. There is striking atrophy of the right amygdala (fat arrow) and hippocampus (thin arrow).](image-url)
often associated with diffuse white matter damage and cerebellar atrophy. Hypoperfusion can also produce hippocampal neuronal loss or severe white matter changes leading to hippocampal sclerosis. There is severe gliosis and neuronal loss in the CA-1 region of the hippocampus and in the subiculum, which present as cognitive decline often with marked memory impairment. It predominantly co-occurs with AD but is also seen associated with frontotemporal lobar degeneration and tauopathies. Dedicated coronal T2 and FLAIR images show decreased size of the hippocampus with increased signal intensity (Fig. 7). There may be bilateral atrophy of the temporal lobes with associated T2 hyperintensity changes in the white matter. It is often accompanied by multiple small infarcts in other brain regions, leukoencephalopathy, or both.

Fig. 6. 61-year-old man with acute-onset amnesia. Axial DWI (A) and T2 (B) MR images show hyperintensity in the anteromedial aspect of the right thalamus (arrows) caused by acute thalamic stroke.

Fig. 7. Dementia caused by global hypoxia in a 54-year-old man. Axial DWI (A) MR image shows restricted diffusion in the cerebral cortex bilaterally (arrowheads), suggestive of diffuse hypoxic injury from hypotension. Follow-up scan performed 2 years later for early signs of dementia shows advanced cortical atrophy for the age of the patient on T2 MR image (B).
SMALL-VESEL VAD (WMLS AND DEMENTIA)

With the advent of MR imaging, diffuse or focal WMLs are detected with higher sensitivity. These lesions are also related to various cognitive decline and VaD. In neuropathology literature, these lesions are described under various synonyms, such as subcortical arteriosclerotic encephalopathy orBinswanger disease, diffuse white matter disease, WMLs, leukoaraiosis, periventricular arteriosclerotic (leuko) encephalopathy or leukomalacia, subcortical vascular encephalopathy, and periventricular lucency.

**Subcortical VaD**

As per the NINDS–AIREN’s diagnostic criteria, small-vessel VaD is classified into 2 types: subcortical and cortical forms.\(^{11,12,27}\) The subcortical form is a classic subcortical VaD (SCVD), whereas the cortical SVD is mostly cerebral amyloid angiopathy (CAA). SCVD is the most common subtype of small-vessel VaD and constitutes approximately 50% of VaD cases.\(^{27,28}\) SCVD is attributed to SVD and is characterized by focal and diffuse ischemic WMLs, lacunar infarcts, and incomplete ischemic injury. All of these disease conditions may coexist.

The risk factors for the SCVD are similar to stroke (smoking, hypertension, diabetes, cholesterol). Cerebral arterial small vessels arise superficially from the subarachnoid circulation as terminations of medium-sized arteries and deeply as arterial perforators from larger vessels at the base of the brain. These vessels supply deep white matter structures. Like the rest of the organs of the body, these cerebral blood vessels also undergo progressive age-related changes. These changes include perivascular collagen deposits, also referred to as microvascular fibrosis and basement membrane thickening, which are mainly seen in the end-arteries and arterioles. The primary target is the small vessels of the white matter; however, the gray matter vessels are affected. Small-vessel changes of fibrohyalinosis in the white matter and angioneurosis and lipohyalnosis in the gray matter, including the basal ganglia and the thalamus. These vessel changes lead to small-vessel cortical microinfarcts, infarcts of the perforating deep small vessels, état criblé (multiple enlarged deep gray matter Virchow–Robin spaces [VRS]), microbleeds, and diffuse WMLs (incomplete infarctions).\(^{27,28}\) Histopathology shows focal areas of white matter demyelination, loss of axons, gliosis, widening of perivascular spaces, and loss of blood–brain–barrier integrity.\(^{27}\) These changes are found mainly in the frontal, parietal, and occipital white matter and in the periventricular areas. Various parenchymal changes lead to a loss of neural integrity and retrograde neuronal dysfunction in the basal ganglia and the cerebral cortices, thereby resulting in vascular parkinsonism and dementia.

Because SVD is a slowly progressive disease, it usually lacks the classic stepwise decline more typical of large-vessel VaD. They commonly present with subcortical cognitive syndrome, which includes executive dysfunction, mental slowness, decision-making problems, poor organizational ability, adaptability difficulties, attention deficit, and apathy. It is attributed to preferential damage to the prefrontal subcortical circuits.\(^{27}\) Because the primary anatomic target of SCVD and AD are different, their clinical cognitive and mental profiles are different. Memory loss is relatively mild in SCVD, but the loss of executive control function is prevalent.

Neuroimaging plays an important role in the diagnosis of SCVD, especially because it is a very slow progressive disease. MR can show changes before the symptoms are evident clinically. The most commonly seen abnormality on MR is a diffuse hyperintensity on T2-weighted imaging (T2WI) primarily in the centrum semiovale and around the ventricles.\(^{27,29}\) Confluent areas of hyperintensities (leukoaraiosis) may also be commonly seen in occipital, periventricular, and sometimes frontal white matter (Fig. 8). On T1WI, corresponding areas may or may not show hypointensity. If these areas are isointense on T1WI, then they represent areas of incomplete infarctions; if they show hypointensity, then they are caused by complete infarction and represent tissue destruction. Ex vacuo dilatation of the ventricles may be seen because of softening of the periventricular white matter. Newer imaging techniques, such as CT or MR perfusion, may show a diffuse decrease in the cerebral blood flow and volume in the cerebral white matter. For the diagnosis of Binswanger disease, it is important to have associated clinical cognitive decline from a previously higher level of functioning in memory and 2 or more cognitive domains, in addition to the white matter changes on neuroimaging (Fig. 9).\(^{30,31}\) The decline must at least be severe enough to interfere with activities of daily living. Without clinical findings, such findings on imaging are to be termed leukoaraiosis.

The second most common imaging finding seen with SVD is focal WMLs. WMLs have been found in 22% of patients younger than 40 years and in 27% to 60% of those patients older than 65 years, whereas in patients with AD and VaD, they are detected by MR in almost 100% of patients.\(^{32}\) The WMLs can be categorized into periventricular WMLs (PVWMLs), which are attached to the
ventricular system, and deep WMLs (DWMLs), which are located in subcortical white matter. On T2/FLAIR images, PVWMLs may be further differentiated into smooth, well-defined hyperintensities versus irregular PVWMLs.32,33 DWMLs and irregular PVWMLs are more likely to be caused by microcystic ischemic lesions. Irregular PVWMLs are more frequently seen with atherosclerosis and thought to be more hemodynamically determined, whereas DWML might be more attributed to SVD, which is seen more commonly with hypertension. Studies have shown that the risk of dementia and the severity of cognitive impairment is preferentially associated with PVWML (Fig. 10), whereas mood disorders were more likely seen with DWML (Fig. 11).32,33

**Lacunes**

Lacunes are defined as focal complete infarcts of deep small vessels that are less than 2 cm in size.22 They are the second most common imaging finding seen in patients with subcortical dementia. Lacunae result from SVD with lumen occlusion secondary to arteriolosclerosis caused by microatheroma and lipohyalinosis or embolism, usually in patients with arterial hypertension.34 These changes are mostly seen in the deep perforators, such as lenticulostriate, thalamoperforating, and long medullary arterioles. Therefore, lacunae are mostly seen in the basal ganglia, the upper two-thirds of the putamen, the internal capsule, the thalamus, the paramedian and lateral regions of the brain stem, the corona radiata, and the centrum semiovale. These regions play an important role in several aspects of cognition. On histopathology, lacunes are often scattered within the areas of pallor in the white matter. They show cavitory and noncavitary infarctions or areas of vacuolation, with a loss or pallor of myelin, loss of axons and oligodendroglia, and areas of reactive astrocytosis, with or without macrophage reaction.

MR imaging is more sensitive than CT for the diagnosis of acute and chronic lacunar infarctions. Signal intensity of a lacunar infarct largely depends on the stage of the infarct. Acute lacunes show a small area of restricted diffusion with corresponding low ADC signal changes. In the chronic stages, these lesions are seen as round, oval, or slitlike, small cavitated infarcts ranging from a few millimeters to 1.5 cm. These lesions are hyperintense on T2 and FLAIR images and remain hypointense on T1WI (Fig. 12). In very late stages, lacunes may be hypointense on FLAIR with an irregular rim of hyperintensity around. A common differential diagnosis includes VRS, which follow CSF signal on all MR imaging sequences. In practice, the 2 forms of subcortical ischemic VaD, lacunae and deep WMLs, are often seen together, presumably because of their common origin.

**Perivascular Spaces**

Perivascular spaces (PVS) or VRS represent subpial interstitial spaces surrounding the penetrating arteries and arterioles.35 They are seen most commonly along the path of lenticulostriate arteries entering the basal ganglia or along the perforating medullary arteries entering the cortical gray matter. Prominent VRS may occur in all age
groups and are regarded as incidental findings without much clinical significance. However, when they are prominent in elderly patients, they indicate the shrinkage of the surrounding white matter. On histopathology, there is no evidence of necrosis, macrophages, or tissue debris in the VRS. Dilated PVS may contain an insignificant and dispersed population of lipid-rich or iron pigment-laden macrophages. Dilatation of the VRS is common in disorders associated with microvascular diseases, and they are as important as periventricular hyperintensity in the scoring of cognitive deficiency. Multiple enlarged VRS in the basal ganglia is called *état criblé* and may present clinically, either with movement disorders or cognitive decline (Fig. 13).  

On MR, the PVS appears oval, with a well-defined, smooth margin that is isointense to CSF on all pulse sequences and demonstrates no enhancement after contrast administration. They are usually bilateral but may be unilateral and are localized at the level of anterior commissure, basal ganglia, cerebral convexity, midbrain, or inferior putamen. The most common differential diagnosis is lacunar infarcts, which are hyperintense on FLAIR and proton-density images.

**Silent Cerebral Infarcts**

Infarcts are defined as silent if they lack strokelike symptoms. Although they are termed *silent strokes*, they do present as subtle deficits in

*Fig. 9.* Binswanger disease in a 67-year-old male patient with cognitive decline. Axial T2 (A, B) and FLAIR (C) MR images show extensive symmetric hyperintensity in the white matter sparing the U fibers (arrows). Increased signal intensity is also noted in the deep gray matter nuclei bilaterally.
physical and cognitive function that commonly go unnoticed. Moreover, the presence of silent infarcts more than doubles the risk of subsequent stroke and dementia. The relationship between silent brain infarcts and the risk of dementia and cognitive decline in the general population has been well established following the Rotterdam Scan study. The study showed that the presence of silent brain infarcts more than doubles the risk of dementia, including AD. Silent brain infarcts were also shown to be the risk factor for mild cognitive impairment in the Cardiovascular Health Study. Silent brain infarcts are common among the general population. They are far more common than strokes, both with respect to prevalence and incidence. The overall prevalence of silent infarct ranges from 8% to 28% and increases with age. Their risk factors are similar to infarction, with hypertension being, by far, the strongest modifiable risk factor.

The cumulative effect of this silent infarct can give rise to deficits in cognitive function. The symptoms totally depend on the area and the white matter connections disrupted, with memory performance being most affected by silent thalamic lesions. WMLs and cortical microinfarcts...
Fig. 12. SVD with lacunes. Axial T2 (A) and FLAIR (B) MR images show diffuse confluent hyperintensity in the white matter with multiple tiny lacunes (arrowheads in A). There is atrophy of the hippocampus bilaterally (arrows in B).

Fig. 13. État criblé and SVD in 71-year-old man with dementia. Axial T2 (A), FLAIR (B), and T1 (C) MR images reveal multiple enlarged PVS in the basal ganglia, which are isointense to the CSF space on all 3 sequences (arrowheads). There is generalized prominence of convexity sulci, ventricular system, and diffuse periventricular white matter hyperintensity caused by ischemic SVD.
from the silent infarctions results in disruption and
degradation of white matter pathways connecting
the cortical (particularly frontal) and subcortical
structures.\textsuperscript{39} It is also presumed that the vascular
lesions somehow also increase the development of
plaques and tangles.

**MICROHEMORRHAGE AND DEMENTIA**

Primary, large, intracerebral hemorrhage is a rare
cause of dementia. A primary bleed can cause
cognitive decline only if they are in a strategic loca-
tion, such as basal ganglia and thalamus. With the
advent of susceptibility-weighted imaging tech-
niques, MR is capable of detecting millimeter-
sized paramagnetic blood products including
hemosiderin stored in macrophages from the
leakage of small blood vessels in the basal ganglia
or subcortical white matter. Microbleeds are
defined as small, rounded, hypointense foci on
T2* or susceptibility-weighted images not attribut-
able to vessels, calcification, or other pathologic
conditions like cavernomas. Microbleeds caused by
sporadic SVD are often central in distribution
involving the basal ganglia, whereas their distribu-
tion is mostly cortical-subcortical (lobar) in specific
disorders, such as CAA.\textsuperscript{40}

**CAA**

CAA has been defined as an amyloid deposition in
the cerebral vessels sufficient to cause vascular
dysfunction, mainly microhemorrhages.\textsuperscript{41,42} CAA
may be either hereditary or sporadic. Sporadic
CAA is a common cerebrovascular pathology of
the elderly and is caused by the deposition of
\(\beta\)-amyloid in the media and adventitia of small-
to medium-sized cerebral arteries.\textsuperscript{41,42} Age is the
strongest risk factor for sporadic occurrence of
CAA. The prevalence of CAA on autopsy is around
2\% at 50 years of age and increases to 74\% to
100\% in patients older than 90 years.\textsuperscript{43} In sporadic
CAA, the apolipoprotein E e2 and e4 alleles are risk
factors: the latter leads to a higher propensity for
\(\beta\)-amyloid 40 to be deposited in vessel
walls.\textsuperscript{41,42,44} Histopathologically, degenerative
vascular changes are mainly seen affecting the
capillaries, arterioles, and small- and medium-
sized arteries of the cerebral cortex, overlying lep-
tomeninges, and cerebellum. White and deep gray
matter vessels are relatively spared. Changes in
the vessel include amyloid deposition, fibrous
thickening of the vessel wall, fibrinoid necrosis,
and leakage of blood through the degenerated
vessel wall.

There are also hereditary forms of amyloidosis,
the most widely studied is the APP gene on chro-
mosome 21 having specific point mutations.\textsuperscript{45} The
age of onset of hereditary CAA is almost 3 de-
cades earlier (30–60 years) to the sporadic aging-
related CAA (60–80 years).\textsuperscript{45,46} In all of these
APP-related CAAs, meningo-cortical arteries are
affected by \(\beta\)-amyloid deposits, leading to neu-
ronal dilatation or thinning of the vessel wall
and to fibrinoid necrosis. Vessels in the deep hemi-
spheric structures and brainstem are relatively
spared.

In both types of CAA, patients may present with
focal neurologic signs, including spasticity, ataxia,
facial paralysis, occasional seizures, and cognitive
impairment often leading to dementia. It is mostly
the subcortical type of dementia. Stroke, a com-
mon feature of sporadic CAA, is slightly less com-
mon in the hereditary type of CAA. Rapid decline
der of cognitive functions is thought to be caused by
diffuse white matter changes. Neuroimaging,
especially MR with susceptibility-weighted im-
ages, plays a vital role in the diagnosis of the
CAA. On T2WI, white matter shows diffuse hyper-
intensities with lacunes caused by ischemia. One
of the main findings is the presence of multiple mi-
crohemorrhages at the corticomedullary junctions
on GRE or susceptibility weighted imaging (SWI)
images (Fig. 14). There may be superficial sidero-
sis caused by cortical bleeds. Patients may also
show large acute or subacute lobar bleeds on CT
or MR.

**Cerebral Autosomal Dominant Arteriopathy
With Subcortical Infarcts and
Leukoencephalopathy**

Cerebral autosomal dominant arteriopathy with
subcortical infarcts and leukoencephalopathy
(CADASIL) is an autosomal dominant arteriopathy
with complete penetrance.\textsuperscript{43} The estimated prev-
ance in Western countries is around 5 cases in
100,000.\textsuperscript{47} Clinical symptoms may be seen as
early as 10 years of age. Migraines, usually with
auras, are the most common symptom. Other
clinical features include transient ischemic at-
tacks, recurrent strokes, depression, ataxia,
cognitive decline, and dementia. CADASIL is
caused by single missense mutations or exon de-
letions in the Notch3 gene on chromosome 19.\textsuperscript{48}
The gene encodes a type 1 transmembrane pro-
tein (Notch3), which is essential during develop-
ment and for regulating cellular differentiation. A
definitive diagnosis requires skin biopsy and ge-
etic testing. Pathologically, the vessels show
severe arteriopathy caused by deposition of the
granular osmophilic material in the media of small
vessels (diameter 100–400 \(\mu\)m).\textsuperscript{49} A loss of
vascular smooth muscle cells in the brain leads
to wall thickening and fibrosis in small- and
medium-sized penetrating arteries. The wall thickening and fibrosis leads to a reduction in both cerebral blood flow and blood volume in the affected white matter with effects on the hemodynamic reserve by decreasing the vasodilatory response. The affected vessels progress to obliteration and/or thrombosis, leading to multiple subcortical infarcts predominantly involving the fronto-temporal white matter and lacunar infarcts, mainly in the basal ganglia.

An MR may show 2 main abnormalities in CADASIL: first, 0.5- to 2.0-cm linear or punctate sharply defined, lacunar infarcts in the periventricular deep white matter, subcortical white matter, external capsule, brainstem, basal ganglia, and thalamus and, second, large, confluent white matter changes predominately in the subcortical regions of the anterior temporal and frontal lobes with involvement of the subcortical U fibers. These changes are often symmetric (Fig. 15). Ribbonlike hyperintensities may also be seen in the external capsule, which are characteristic for CADASIL. Temporal white matter and paramedian superior frontal white matter regions and arcuate fiber involvement is the major finding differentiating CADASIL fromBinswanger disease. An MR may also show areas of low signal intensity within the deep gray matter nuclei on T2 and GRE images thought to be caused by increased iron deposition, possibly resulting from disturbed axonal iron transport.

**Fig. 14.** Cerebral amyloid angiopathy. Axial CT (A) image shows generalized prominence of convexity sulci, dilation of ventricular system, and diffuse hypodensity in the white matter (arrows). Axial FLAIR (B) MR image shows global cerebral atrophy with diffuse white matter hyperintensity (arrows) caused by ischemic SVD. Axial SWI (C) MR image shows multiple hypointensities in the cortical and subcortical region (arrows), suggestive of microhemorrhages.
SUMMARY
As people live longer, there is a corresponding increase in neurodegenerative disorders and dementia. More than 24.3 million people are currently estimated to have dementia, and 4.6 million new cases are diagnosed each year. It is predicted that worldwide, a new case of dementia is diagnosed every 7 seconds. When atrophy is seen on imaging in adult patients, it does not necessarily represent AD. Many cases of dementia or cognitive decline could be caused by reversible or preventable disease, such as VaD. This article familiarizes the physician with various types of vascular lesions leading to dementia and cognitive decline and their imaging appearances. Neuroimaging plays an important role in identifying vascular lesions of the brain very early, even before the clinical manifestation of the cognitive decline symptoms and, thus, can help to prevent or delay the symptoms related to the various vascular pathologic conditions.

REFERENCES


